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APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO	CONFIRMATION NO
09 412,297	10 05 1999	KANG, HSU	3100 008C0	9486

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QUINE INTELLECTUAL PROPERTY LAW GROUP, P.C.  
P O BOX 458  
ALAMEDA, CA 94501

EXAMINER
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FORD, VANESSA L

ART UNIT	PAPER NUMBER
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1645  
DATE MAILED: 07 15 2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

## Office Action Summary

Application No.

09/412,297

Examiner

Vanessa L. Ford

Applicant(s)

TING, KANG

Art Unit

1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.1(b)(4). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply, other than statutory minimum of thirty (30) days, will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply, and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) Responsive to communication(s) filed on 24 April 2003.
- 2a) This action is FINAL.      2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) Claim(s) 1,2 and 8-12 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) Claim(s) \_\_\_\_\_ is/are allowed.
- 6) Claim(s) 1,2 and 8-12 is/are rejected.
- 7) Claim(s) \_\_\_\_\_ is/are objected to.
- 8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on 26 March 2003 is/are: a) accepted or b) objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) The proposed drawing correction filed on \_\_\_\_\_ is: a) approved b) disapproved by the Examiner.  
If approved, corrected drawings are required in reply to this Office action.
- 12) The oath or declaration is objected to by the Examiner.

### Priority under 35 U.S.C. §§ 119 and 120

- 13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All b) Some \* c) None of:  
1) Certified copies of the priority documents have been received.  
2) Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
3) Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).  
a) The translation of the foreign language provisional application has been received.
- 15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

### Attachment(s)

- 1) Notice of References Cited (PTO-892)      4) Interview Summary (PTO-413) Paper No(s) \_\_\_\_\_.  
2) Notice of Draftsperson's Patent Drawing Review (PTO-948)      5) Notice of Informal Patent Application (PTO-152)  
3) Information Disclosure Statement(s) (PTO-1449) Paper No(s) \_\_\_\_\_.      6) Other: \_\_\_\_\_

**DETAILED ACTION**

1. The request filed on 24 April 2003 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/412, 297 is acceptable and a CPA has been established. An action on the CPA follows. Claims 1-2 and 8-12 are pending and under examination.
  
2. Applicant's response and Declaration submitted under 37 U.S.C. 1.131 with an accompanying Exhibit is acknowledged.

***Rejections Withdrawn***

3. In view of Applicant's response the following rejections are withdrawn:
  - a) Rejection under 35 U.S.C. 102(b) of claims 1 and 8-12, paragraph 6, pages 3-5 of the previous Office action.
  - b) Rejection under 35 U.S.C. 103(a) of claim 2, paragraph 7, pages 6-8 of the previous Office action.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-2 and 8-12 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification has not provided enablement for a method of screening for an agent that modulates bone mineralization in any bone tissue said method comprises contacting the any cell containing a Nell-1 gene with a test agent and detecting an expression level of said Nell-1 gene in the contacted cell where a difference in the expression level of Nell-1 in the contacted cell compared to an expression level of Nell-1 in a cell that is not contacted indicates that said test agent is an agent that modulates bone mineralization.

The specification teaches that Nell-1 expression is increased in fetal calvarial cells associated with bone formation in calvarial osteoblast-like cells in the fetus (page 42). The specification teaches that premature cranial suture closure as seen in craniosynostosis (CS) may be due to overproduction of cranial bone and therefore possibly but not definitively associated with the overexpression of the Nell-1 molecule (page 42). The specification teaches that Nell-1 mRNA was faintly expressed from day 14 of gestation with mild increase over gestation period and at day 14 is the time point when fetal calvaria starts to mineralize (page 42). The specification states "as a possible role of Nell-1, these proteins may act as a modulator interacting with other growth factors. The specification teaches that the Nell-1 protein may execute their unidentified functions extracellularly by interacting with some members of the TGF $\beta$  superfamily (page 43). The specification teaches that since TGF $\beta$ -1 is known as a regulator of osteogenesis, Nell-1's effect in enhancing mineralization may be related to its interaction with the TGF $\beta$  superfamily (page 43). The specification speculates on the function of Nell-1 based on the observation that it's expression is increased in fetal

calvarial osteoblast-like cells. However, one skilled in the art would have reason to doubt Applicant's assertion that you could use any cell containing the Nell-1 gene to screen for modulators of bone mineralization for following reasons: The specification has not enabled for a method of screening for an agent that modulates bone mineralization in any bone tissue contacting any cell containing a Nell-1 gene with a test agent. The specification concludes that "Nell-1 is associated with bone mineralization in calvarial osteoblast-like cells" (i.e. cranial intramembranous bone and neural tissue) based on its increased expression (page 41). The specification fails to teach how the Nell-1 gene actually functions in adult and/or non-neural cells, which would be encompassed by the claimed method. One of skill in the art cannot conclude that the claimed method for screening for an agent that modulates bone mineralization in any bone tissue by contacting any cell that comprises the Nell-1 gene can be obtained by the information contained in the instant disclosure.

The teachings cited below indicate that the actual functions of Nell were unknown to the art and indicate that Nell-1 has no function in the vast majority of bone mineralization.

Watanabe et al (*Genomics* 38, 273-276, 1996) teach that Nell-1 was isolated from a human fetal brain cDNA library. Watanabe et al teach that Nell-1 contained open reading frames encoding 810 amino acids (see the Abstract). Watanabe et al teach that Nell-1 seemed to be very weakly expressed in brain and kidney of fetus and adult tissues there are irrelevant to bone mineralization (page 274 , 1<sup>st</sup> column). Watanabe et al teach that it is difficult to assess Nell-1 expression and this might mean that only a

small specific population of cells expressed this gene (page 276, 1<sup>st</sup> column). Ting et al (*Journal of Bone and Mineral Research, Volume 14, No. 1, 1999*) teach that human Nell-1 was localized primarily in the mesenchymal cells and osteoblasts at the osteogenic front (see the Abstract). Ting et al teaches that human multi-organ tissue mRNA blot showed that Nell-1 was specifically expressed in fetal brain but not fetal, liver or lung (see the Abstract). Ting et al teach that Nell-1 is preferentially expressed in cranial intramembranous bone and neural tissue is up-regulated during unilateral premature closure of the coronal suture (see the Abstract). Ting et al teach that the Nell-1 gene seems to be expressed in a tissue- and time specific fashion (page 86, 1<sup>st</sup> column). Ting et al teach that Nell-1 may be a molecule that is differentially expressed in craniofacial intramembranous bone but not in endochondral bone (page 87, 2<sup>nd</sup> column). Nell-1 expression does not correlate with bone mineralization in general, only with bone mineralization at the osteogenic front. Ting et al teaches that the precise role of the Nell-1 gene is unknown (see the Abstract). Kuroda et al (*Biochemical and Biophysical Research Communications, 265, 752-757, 1999*) suggests that the Nell proteins possess potential oncogenic activities in non-neural tissues (page 756, 2<sup>nd</sup> col.). Kuroda et al teach that the function of the Nell proteins is unidentified (page 756, 2<sup>nd</sup> col.). The cited art has taught that Nell-1 has other potential functions in tissues irrelevant to bone formation. Therefore, it is not clear that an agent that modulates these tissues would affect bone mineralization. Zhang et al (*The Journal of Clinical Investigation, September 2002, Vol. 110, No. 6*) teach that the Nell-1 protein molecule is overexpressed during premature cranial suture closure in patients with craniosynostosis

(CS) (see the Abstract). Zhang et al teach that *in vitro* Nell-1 overexpression accelerated calvarial osteoblast differentiation and mineralization under normal human conditions in transgenic mice. Zhang et al specifically teach overexpressing Nell-1 protransgenic mice provided for anomalies restricted to calvarial bone, despite generalized, non-tissue specific overexpression of Nell-1. As such, there is no evidence for a role of Nell-1 in bone mineralization in general in the fetus or bone mineralization in the adult. It is clear that any cell cannot be used for screening because Nell-1 plays no role in bone mineralization in the vast majority of cells capable of forming bone in the fetus and adult. Therefore, one could not just use "any cell" possessing the Nell-1 gene to screen for modulators. Additionally, to screen for "inhibitors" one must have a cell that expresses Nell-1 not merely having the gene. Zhang et al teach that Nell-1 most likely influences osteoblast differentiation, however the molecular mechanism is unknown. Zhang et al teach that Nell-1 overexpression may not reflect the true physiological function of Nell-1 but rather the effect of Nell-1 overexpression on other thrombospondin-like molecules (page 869, 2<sup>nd</sup> col). Zhang et al teach that Nell-1 overexpression induces intramembranous bone formation in cranial sutures and may lead to the calvarial overgrowth/overlap and subsequent premature suture closure (page 870, 1<sup>st</sup> col). Zhang et al teach that Nell-1 is a relatively newly discovered molecule with unknown function (page 867, 2<sup>nd</sup> col).

The cited art teaches that Nell-1 is a secreted protein, that Nell-1 is over-expressed during premature cranial suture closure in patients with craniosynostosis (CS) and that Nell-1 may execute their unidentified functions extracellularly by

interacting with some members of the TGF $\beta$  superfamily. The cited art teaches that Nell-1 induces intramembranous bone formation but not in endochondral bone and that Nell-1 overexpression may not reflect the true physiological function of Nell-1 but rather the effect of Nell-1 overexpression on other thrombospondin-like molecules and is not involved in all types of bone mineralization. However, the art references cited conclude that Nell-1 is a relatively newly discovered molecule with unknown function.

Factors to be considered in determining whether undue experimentation is required are set forth in In re Wands 8 USPQ2d 1400. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

There is lack of enablement for the use of method for screening an agent that modulates bone mineralization in any bone tissue contacting any cell containing a Nell-1 gene (not necessarily expressed) with a test agent comprising contacting a cell containing a Nell-1 gene with a test agent and detecting an expression level of said Nell-1 gene in the contacted cell where a difference in the expression level of Nell-1 in a cell is not contacted indicates that said test agent is an agent that modulates bone mineralization. The specification only focuses on the enhancement of Nell-1 in fetal calvarial osteoblastic cells (see Example 1 of the specification). The cited art has taught that Nell-1 may only be associated with bone mineralization in intramembranous bone formation but not in endochondral bone. Therefore, the specification is does not provide

enablement for a method for screening an agent that modulates bone mineralization in any bone tissue comprising contacting any cell containing the Nell-1 gene when the cited art teaches that Nell-1 is time and tissue specific and the Nell proteins possess potential oncogenic activities in non-neural tissues. The cited art further teaches that overexpression of may not reflect the true physiological function of Nell-1 but rather the effect of Nell-1 overexpression on other thrombospondin-like molecules. Therefore, one of skill in the art could not conclude that the Nell-1 gene could be used to screen for agents that modulate bone mineralization in any bone tissue when the instant specification and the cited art only teaches that Nell-1 may be associated with intramembranous bone formation in fetal calvarial osteoblastic cells. It is determined that there are no working examples commensurate with the claims that demonstrate that a reduction in Nell expression corresponds with decreased bone mineralization and there is limited guidance provided in the specification as to how to use the claimed method since the cited art has taught that the precise function of Nell-1 is unknown. The skilled artisan is forced into undue experimentation to practice (make and use) the invention as is broadly claimed.

5. No claims are allowed.

***Conclusion***

6. Any inquiry of the general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Office Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for the Group 1600 is (703) 308-4242.

Any inquiry concerning this communication from the examiner should be directed to Vanessa L. Ford, whose telephone number is (703) 308-4735. The examiner can normally be reached on Monday - Friday from 7:30 AM to 4:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached at (703) 308-3909.

  
Vanessa L. Ford  
Biotechnology Patent Examiner  
July 10, 2003

*Patricia A. Duffy*  
PATRICIA A. DUFFY  
PRIMARY EXAMINER